REMARKS

Claims 1- 13, 15, 16 and 18-30 are pending in the application. Claim 17 has been canceled and claim 14 has been canceled in this amendment. Claims 1-9 and 18-29 have been withdrawn.

Claim 10 has been amended by deleting the article "a" occurring before "brain-derived" and "nerve growth factor." This claim has also been amended by inserting the phrase "for regenerating periodontal tissues" after "neurotrophic factor" in line 2. Support for this amendment can be found in the Specification in paragraphs [0020] – [0023]. Claim 10 has been further amended by inserting ", per tooth or defect of furcation," immediately after "effective amount" in line 2. Support for this can be found in claim 30. The phrase "a biodegradable protein material" replaces "an absorbent material" in line 3; support for this amendment can be found in the Specification in paragraph [0059]. Lastly, the subject matter of claim 14 has been incorporated into claim 10.

No new matter has been added.

Rejections Under 35 USC § 112, Second Paragraph

The Examiner has rejected claim 10 as vague and indefinite for recitation of the phrases "a brain-derived neurotrophic factor" and "a nerve growth factor." The Examiner contends that use of the article "a" in these phrases make it unclear whether a broad class of neruotrophic factors is being claimed or simply "brain-derived neurotrophic factor" and "nerve growth factor."

Applicants have deleted the article "a" from claim 10, as suggested by the Examiner, thereby overcoming the rejections.

The Examiner has rejected claims 10 and 30 for recitation of "a periodontal transplant which comprises a therapeutically effective amount of a neurotrophic factor" without specifying what the therapeutically effective amount is effective to do.

Applicants have amended the claims to clearly indicate the treatment use of the therapeutic amount, thereby overcoming the rejections.

The Examiner has rejected claim 30 for lack of antecedent basis for the phrase "wherein the therapeutically effective amount is in the range of 1 X 10-12 to 1 X 10-3 g per tooth or defect of furcation." Applicants have amended claim 10 to include "per tooth or defect of furcation," thereby overcoming the rejection.

Rejections Under 35 USC § 112, First Paragraph (Enablement)

The Examiner has rejected claim 14 for recitation of the term "prevents" and failing to enable the use of the invention to fully prevent apical invasion of gingival epithelium along the dental root surface.

Applicants have canceled claim 14, thereby obviating the rejection.

Rejections Under 35 USC § 103

The Examiner has rejected claims 10-13, 15, 16 and 30 as obvious over Kirker-Head in view of Wikesjö, Tsuboi et al., Jurihara et al. and Harada et al. The Examiner contends that Kirker-Head teaches that BMPs are useful for treatment of periodontal disease including regeneration of periodontal ligament, bone, cementum and gingiva and suggests to the skilled artisan that a periodontal transplant containing a growth factor and an absorbent material is capable of regenerating the periodontal ligament, bone, cementum and repair dentine formation and maintain pulp vitality. The Examiner admits that Kirker-Head does not suggest that BMP-2 regenerates alveolar bone when combined with an absorbable collagen matrix, but relies on Wikesjö's report regarding PGA-TMC/BMP-2 to fill this void. The Examiner also admits that

the Kirker-Head reference does not teach a transplant comprising BDNF and here contends that the teachings of Tsuboi et al., Jurihara et al. and Harada et al. provide the teaching omitted by Kirker-Head. Nonetheless, the Examiner concludes that the instant invention is obvious over a combination of the cited references. Applicants respectfully traverse.

One of skill in the art would not have been motivated to combine the cited references to obtain the claimed invention. In addition, even if the skilled artisan decided to try such a combination, they would not have had a reasonable expectation of success in generating the instant invention.

As stated in the accompanying Declaration, while the Kirker-Head reference includes a sentence on page 77 which states "the BMP's ability to enhance periodontal tissue regeneration has been studied," the Kirker-Head reference actually discloses effects of BMP-2 on skeletal tissue formation, not on periodontal tissue.

In addition, the secondary reference on which the Examiner relies, Wikesjö, does not convince the skilled artisan that periodontal tissue can be regenerated using the Wikesjö methods because ankylosis is produced in the process. The Wikesjö reference itself acknowledges this fact. Furthermore, all but one of the six references which mention ankylosis that are cited by Kirker-Head in support of the statement on page 77 indicate that ankylosis was present after treatment with BMPs. This is important because periodontal tissue regeneration is understood by those of skill in the art to exclude ankylosis, as noted in the Declaration.

Given that the data presented for the effect of BMPs on regeneration of periodontal tissue showed the presence of ankylosis, and that significant research time and effort had been invested in exploring the effect of BMPs on periodontal tissue, the skilled artisan would have had little motivation to substitute a neurotrophic factor for the BMP. While the Tsuboi et al., Kurihara et al. and Harada et al. references make general statements as to the expression of neurotrophic factors in periodontal tissues, no definitive examples showing the criticality of BDNF or other neurotrophic factors is shown. Consequently, while a skilled artisan might arguably try replacing BMPs with a neurotrophic factor because it is expressed in periodontal tissues, there would have

been no expectation of success associated with producing a periodontal transplant that would regenerate normal periodontal tissues comprising both hard tissues and soft tissues.

Lastly, there is no teaching in the references suggesting that only particular types of bioabsorbable carriers are capable of accomplishing the goal of regenerating normal periodontal tissue. As can be seen from the experiment presented in the Declaration, while PLGA is a bioabsorbable carrier, it is incapable of regenerating periodontal tissue. Thus, the finding that the combination of a neurotrophic factor and a biodegradable protein material can effect regeneration of normal periodontal tissue was not predictable from the prior art references and is nonobvious over the cited art.

In view of the above, Applicants respectfully request reconsideration and removal of the rejection.

Conclusion

Applicants submit that all of the claims define non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to our Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under § 1.17; particularly, extension of time fees.

Dated: November 24, 2009

Respectfully submitted,

#47,604

By _____
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PATENT
0230-0245PUS1

IN THE U.S. PATENT AND TRADEMARK OFFICE

APPLICANT:	Hidemi KURIHARA et al.	CONF:	2459
SERIAL NO.:	10/571,069	GROUP:	1649
FILED:	December 7, 2006	EXAMINER:	C. M. Borgeest

FOR: THERAPEUTIC AGENT AND THERAPEUTIC METHOD FOR PERIODONTAL DISEASES AND PULPAL DISEASES

DECLARATION SUBMITTED UNDER 37 C.F.R. § 1.132

Honorable Commissioner
Of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

November 24, 2009

Sir:

I, Dr. Hidemi KURIHARA of the Department of Periodontal Medicine, Division of Frontier Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, Japan, do hereby declare the following:

I have attached a copy of my curriculum vitae to this Declaration.

I am Professor and chair of Department of periodontal medicine and have worked in this field for 30 years.

I am one of the inventors of the above referenced patent application.

I am familiar with the application, as well as the development, usages and properties of polymer compounds.

I have read and understand the subject matter of the Office Action of June 24, 2009.

The following comments are offered in support of the patentability of the instant invention.

The Examiner states that the Kirker-Head reference makes obvious the 10/571,069 application when combined with the Wikesjö, Tsuboi et al., Kurihara et al. and Harada et al. references. It seems that the Examiner is arguing that when combined, these references suggest making a periodontal transplant containing a neurotrophic growth factor and an absorbent material to treat periodontal disease. I disagree.

First, I believe that it is important to clearly understand the teachings of the various references. With this in mind, I would like to first call attention to the fact that while the Kirker-Head reference includes a sentence "the BMP's ability to enhance periodontal tissue regeneration has been studied," the reference actually discloses effects of BMP-2 on skeletal tissue formation.

Next, the Wikesjö reference includes a description on page 635 regarding cementum regeneration which states "limited cementum regeneration was observed for PGA-TMC/rhBMP-2 and PGA-TMC control sites." From our observation of the figures and tables in the Wikesjö reference, however, periodontal tissue regeneration was not successfully achieved. It is evident from the data of week 8 post-surgery (see Tables 1 and 2) and week 24 post-surgery (see Tables 3 and 4) that there were 100% ankylosis and root resorption. Figure 7 also shows ankylosis. Furthermore, the Wikesjö reference states on page 635 that "ankylosis compromised regeneration in sites receiving PGA-TMC/rhBMP-2." Therefore, although MBP-2 combined with an appropriate carrier material could potentially be used for supporting alveolar bone formation, it also appears to cause a healing aberration of periodontal tissue as a whole due to ankylosis (i.e. a bony attachment without restoration of pericementum and cementum) caused by BMPs.

Periodontal tissue regeneration by definition means reconstituting healthy periodontal tissue, i.e. to restore normal periodontal tissues including cementum, alveolar bone,

periodontal ligament and so on, at a site where periodontal tissue had been missing without any indication of ankylosis. Consequently, although the cited journal references seemingly imply that BMP enhances periodontal tissue regeneration, they actually do not provide a plausible result to show that periodontal tissue regeneration was achieved in a true sense. To the skilled artisan reading the references, the results shown do not support normal periodontal tissue regeneration – quite the opposite. That is, neither the Kirker-Head reference nor the Wikesjö reference teach regeneration of the periodontal tissue including a complex of both soft and hard tissues.

This is in contrast to the information and data presented in application 10/571,069, which has achieved periodontal tissue regeneration in a true sense. Here the inventors have obtained *in vitro* data to show that a neurotrophic factor such as BDNF enhances generation of collagen in soft tissues and have further shown through in vivo data that alveolar bone as well as cementum and periodontal ligament were regenerated without the occurrence of ankylosis.

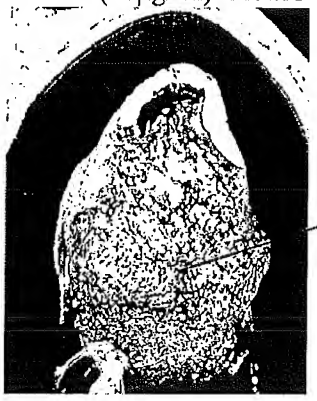
It seems that the Examiner also thinks that the invention described in application 10/571,069 is obvious because the Kirker-Head reference teaches that sponges imbued with BMPs enhance osseointegration and strengthen bone as well as regenerate periodontal tissues, and that BDNF is among the known options that could be used instead of BMPs to treat periodontal disease. But the effect produced by BDNF when combined with an appropriate carrier material is more subtle than the Examiner implies, and this effect is not disclosed or suggested by the teachings of Tsuboi, Kurihara and Harada which indicate that BDNF could be used instead of BMPs.

For example, while Tsuboi and Kurihara each indicate the ability of BDNF to enhance proliferation or DNA synthesis of periodontal ligament cells, these references are silent with respect to any action of BDNF on the growth of gingival epithelium cells. However application 10/571,069 discloses that while a neurotrophic factor such as BDNF induces proliferation of periodontal ligament cells, it does not induce proliferation of gingival epithelium cells, and thus inhibits invasion of epithelium into a lesion of periodontal

tissue defect. This growth of periodontal ligament, when accompanied by inhibition of epithelium invasion, means that a neurotrophic factor such as BDNF contributes to maintaining space for the recovery of a normal periodontal tissue state. This information, which is critical to the 10/571,069 application, is not disclosed in any of the references; that is, none of the cited references disclose that neurotrophic factors, including BDNF, are effective in regenerating normal periodontal tissues comprising both hard tissues and soft tissues.

In addition, having a bioresorbable material combined with an active ingredient (i.e. a neurotrophic factor such as BDNF) is also important for the periodontal transplant to effectively exert its function to regenerate periodontal tissues and to reduce the apical invasion of gingival epithelium along the dental root surface. For example, when poly (lactic-co-glycolic acid) [PLGA] was used as a carrier, periodontal tissue regeneration was not observed (see Figure 1).

Fig.1 BDNF(50μg/ml)+PLGA



The disclosure of the 10/571,069 application shows that biodegradable protein materials provide the advantageous effect of producing normal regenerated periodontal tissue. On the other hand, Wikesjö appears to suggest that any space-providing, bioabsorbable carrier material is suitable, even though the tissue regenerated using PGA-TMC is not normal.

To summarize, it is my opinion that the skilled artisan would not have had a reasonable expectation of success in producing a periodontal transplant capable of regenerating normal periodontal tissues without anklyosis by combining the references cited by the Examiner in the Office Action of June 24, 2009.

The undersigned hereby declares that all statements made herein based upon knowledge are true, and that all statements made based upon information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

DATED: Nov. 24, 2009

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(2) Scientific bibliography

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(3) Honors and awards:

1985-present,	Councilor, The Japanese Society of Conservative Dentistry
1992-present,	Councilor, The Japanese Society of Periodontology
1992	The grant from Ryobi Teien Memorial Foundation
1994	The grant from Kobayashi Magobe Memorial Medical Foundation
1995	The first prize of Award in research section of 5th IAP meeting
1997	The fourth prize of Award in research section of 6th IAP meeting
2005	One of the top ten downloaded papers of Biochemical Communications in 2005, Elsevier Pub.
2006-present,	Executive Director, Japanese Association for Dental Science
2006-present	Executive director, Japan Endodontic Association
2007-present,	Vice President, The Japanese Society for Evidence and the Dental Professional
2009	R. Earl Robinson Periodontal Regeneration Award, American Academy of Periodontology

(4) Member of editorial boards:
Journal of the Japanese Society of Periodontology
Journal of Dental Research, 1999-2003

(5) Appointments

2000-2002,	Vice director, Hiroshima University Dental Hospital
2002-2003,	Director, Hiroshima University Dental Hospital
2003-2004,	Vice director, Hiroshima University Hospital
2004-2008,	Dean, Faculty of Dentistry, Hiroshima University
2008-2009,	Vice Executive (Community Collaboration), Hiroshima University